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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/584,781	05/09/2007	Sungho Jin	15977-34	7355

28221 7590 08/27/2010

PATENT DOCKET ADMINISTRATOR
LOWENSTEIN SANDLER PC
65 LIVINGSTON AVENUE
ROSELAND, NJ 07068

EXAMINER	
REDDIG, PETER J	

ART UNIT	PAPER NUMBER
1642	

MAIL DATE	DELIVERY MODE
08/27/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/584,781	JIN ET AL.	
	Examiner	Art Unit	
	PETER J. REDDIG	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 May 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13 and 15-25* is/are pending in the application.

4a) Of the above claim(s) *18-20, 23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13,15-17,21,22,24 and 25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The Amendment filed May 26, 2010, in response to the Office Action of December 30, 2009 is acknowledged and has been entered. Previously pending claim 14 has been cancelled, claims 1, 3, 16 and 17 have been amended. Claims 1-13 and 15-25 are pending. Claims 18-20, 23 were previously withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions. Claims 1-13, 15-17, 21, 22, 24, and 25 are currently under consideration.

Rejections Maintained

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

2. Claims 1-9, 13 and 21 remain rejected under 35 U.S.C. 103(a) as being unpatentable over WO 01/17611 A1 (Fredriksson et al. March 13, 2001), in view of USPN 6,231,496 (Wilk et al. May 15, 2001) for the reasons set forth in section 7 of the Office Action of 12/30/2009, which are set forth below.

WO 01/17611 A 1 teaches using magnetic nano-particles to damage and destroy cell structures with alternating magnetic field by shear forces. WO 01/17611 A1 teaches coating the particles with an antibody, a bio-compatible material. WO 01/17611 A1 teaches using two magnetic fields and inducing heat hysteresis and structural damage to the cells. See p. 2-5. Figs. 1-3, and claims 1-10. WO 01/17611 A1 teaches that the direction of the magnetic field is alternated, which will alternate the directions of the particles, i.e. it will oscillate. See p. 4. Given that the nanoparticles claimed encompass spherical particles which have no predefined orientation, lateral oscillation encompasses any oscillation.

WO 01/17611 A1 teaches as set forth above and using an alternating magnetic field up to 30 MhZ. WO 01/17611 A1 does not teach delivery of medication, injection of the particles, magnetic nanoparticles elongated long one dimension and rotating the elongated particles at a frequency in the range of 1 Hz to 500 Hz.

USPN 6,231,496 teach using magnetized metal particles that are advantageously tapered to form a sharp end for sterilization and cancer treatment by injecting the particles and orienting the particles with a magnet and pulling them into the tissue with a magnet. See cols. 1 and 2 and claims 1-21. USPN 6,231,496 teaches coating the particles with an irritant for treatment and antibiotics and anti-growth factor. See col. 7-lines 1-5 and claims 1-21

It would have been *prima facie* obvious at the time the invention was made and one of skill in the art would have be motivated to combine the teachings of WO 01/17611 and USPN 6,231,496, and make and use elongated magnetic nano-particles that have a tapered or sharp end as described by USPN 6,231,496 to enhance the shearing effect of cell disruption of the method WO 01/17611. Additionally, given that WO 01/17611 A1 teaches as using an alternating magnetic field up to 30 MhZ, the optimum suitable frequency ranges to rotate the nanoparticles may be obtained by routine experimentation, absent a showing of criticality or unexpected results. Furthermore, the addition of medication to the particles for treatment and injection of the particles would have been obvious as the coating particles with medicine for treatment and injection of therapeutic agents are routine method is the art for medical treatment as shown by USPN 6,231,496.

Applicants argue that the combined teachings of Fredriksson et al. and Wilk et al. fail to obviate the method of inducing structural damage in a target cell as presently claimed. Pursuant to MPEP § 2142, to establish a prima facie case of obviousness, and thus sustain the rejection of a claim under 35 U.S.C. § 103(a), there must be a clear articulation of the reasons why Applicants' claimed invention would have been obvious. *KSR International Co.v. Tefleflex Inc., 550 U.S. 398 (2007)*. The Supreme Court in KSR has further noted that an analysis supporting a rejection under 35 U.S.C. § 103(a) should be made explicit. Therefore, it is clear that an obviousness rejection "cannot be sustained win mere conclusory statements; instead, there must be some articulated reasoning win some rational underpinning to support the legal conclusion of obviousness." *In re Kahn* 441 F.3d 977 (Fed. Cir. 2006). Moreover:, "[t]o support the conclusion that the claimed invention is directed to obvious subject matter, either the references must expressly or impliedly suggest the claimed invention or the examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been: obvious in light of the teachings of the references." MPEP § 706.02(j).

Applicants argue that, as admitted by the Examiner, Fredriksson et al. and Wilk et al. fail to describe applying an AC magnetic field at a frequency in the range 1 Hz to 500 Hz. See Office Action at page 10. However, to support his position, the Examiner states that since Fredriksson et al. "teaches using an alternating magnetic field up to 30 MHz, the: optimum suitable frequency ranges to rotate the nanoparticles may be obtained by routine experimentation, absent a showing of criticality or unexpected results." Id.

Applicants argue that the mere mention in Fredriksson et al. of an alternating magnetic field up to 30 MHz fails to obviate the low magnetic field at a specific frequency range of I Hz to 500 Hz, as presently claimed. By way of the present invention, the inventors have exploited the characteristics of the effect of varying frequencies of the magnetic field as applied to the particles, particularly the characteristics that: magnetic hyperthermia results with a high frequency (see, e.g., *Specification* at paragraphs [[0024] and [0037]), while magneto-mechanical destruction results with a much lower frequency (see, e.g., *Specification* at paragraph [0036]). Applicants argue that thus, the inventors have discovered that it is possible to have magneto-mechanical destruction of the cells without inducing magnetic hyperthermia by applying a low frequency magnetic field. The beneficial nature of applying a low frequency is neither taught nor suggested by the cited art.

Applicants argue that a 30 MHz frequency mentioned in Fredriksson et al. is 60,000 times greater than the highest frequency of the claimed range, i.e., 500 Hz. and 30,000,000 times greater than the lowest frequency of the claimed range, i.e., 1 Hz.

Applicants argue that it would take a vast amount of undue experimentation to derive the claimed frequency range from the frequency mentioned in Fredriksson et al., particularly one that is 60,000-30,000,000 times greater than claimed range,

Accordingly, Applicants argue that the combination of Fredriksson et al. and Wilk et al. fail to obviate the present claims and respectfully request that the rejection under 35 U.S.C. § 103(a) be removed.

Applicants' arguments have been considered, but have not been found persuasive. First Fredriksson's disclosure of an alternating magnetic field up to 30 MhZ makes that claimed range of 1 Hz to 500 Hz obvious as the claimed range lies within the prior art range.

> In the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a prima facie case of obviousness exists. *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed.Cir. 1990). See MPEP 2144.05 (I)

Thus, although the endpoint of the range is much higher than the currently claimed range, the claimed range is within the prior art range and, thus, is obvious. Additionally, whether or not it is possible to have magneto-mechanical destruction of the cells without inducing magnetic hyperthermia by applying a low frequency magnetic field, it is noted that said features upon which applicant relies are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Furthermore, this effect would inherently occur when the claimed magnetic fields are applied and the claiming of unknown property which is inherently present does not make the claim patentable. See MPEP 2112 (I). Additionally, the instant specification has not taught that treating at 1 Hz to 500 Hz provides any particular beneficial or unexpected results; rather that it is simply a preferred treatment range. See [0036] of the published application. Thus, for the reasons previously set forth and above the rejection is maintained.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claims 1, 2, 5-9, 15, 21, and 24 are rejected under 35 U.S.C. 102(b) as being anticipated by USPN 6,470,220 (Krauss et al. Oct. 22, 2002) evidenced by World Health Organization (What are electromagnetic fields?, 2010)

Krauss et al. teach detecting and treating cancer by 1) Binding a cancer-binding agent to a magnetic nano- or micro-particle; 2) Delivery of the magnetic particles to the tumor site by introducing the cancer-binding magnetic particles into the subject bloodstream by injection; 3) Locate tumor(s) by detecting and localizing regions of abnormal uptake and concentration of magnetic particles; and, 4) Inducing tumor necrosis by rapid and focused thermal deposition with minimal collateral damage. See Col.3 and 4. Krauss et al. teach using a combination of multiple alternating magnetic fields with field frequencies as low as 100 Hz to generate a stirring action and rotational heating to induce necrosis in tumor cells. See claim 1, Summary of The Invention, col. 3, 4, 6, 13 and 14. Krauss et al. teach coating the particles with biocompatible materials like glass, buckyballs, liposomes, conjugated to antibodies or peptides (which are polymers of amino acids) for targeting, as such anti-Her2 antibodies. See col. 5, ¶ bridging col. 12 and 13.

It is noted that that the electromagnetic fields with a frequency used by Krauss et al. are AC magnetic fields as they vary over time. See p. 2 of World Health Organization- *How do static fields differ from time-varying fields?*

Although the reference does not specifically state that the magnetic field laterally oscillates the nanoparticles to structurally damage the target cell, given that a claimed frequency and magnetic nano-particles are used, the claimed method appears to be the same as the prior art method, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the method of the prior art does not possess the same material, structural and functional characteristics of the claimed method. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed method is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 3, 4, 16, 17, 22, and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over USPN 6,470,220 (Krauss et al. Oct. 22, 2002) evidenced by World Health Organization (What are electromagnetic fields?, 2010), as applied to claims 1, 2, 5-9, 15, 21, and 24 above, in view of Chung et al. (J. Controlled Release 2000 65: 93-103, previously cited), in view of Jordan et al. (J. Magnetism and Magnetic Materials, 2001 225:118-126, IDS), and in view of Tannock, I.F. (*Experimental Chemotherapy*, Ch. 19-p. 338 and 352-359, in The Basic Science Of Oncology Tannock and Hill, eds., New York 1992).

Krauss et al. teach as set forth above, and teach that MRI has potential for breast cancer detection. See col. 1. Krauss et al. do not teach, particles that comprise further comprise medication or a heat sensitive reservoir of medication, that the application of the magnetic field to the nanoparticles provides heat to effect delivery of the medication, or confirming the contact with MRI imaging.

Chung et al. teach thermo-sensitive polymeric micelles comprised of AB block copolymers of PIPAAm with either poly(butly methacrylate or polystyrene for the thermo-responsive drug delivery of adriamycin to cells, see Abstract, Fig. 4 and 5 and table 1. Chung et al. teach that the thermo-responsiveness of the micelles can increase the targeting efficiency via a stimuli-responsive targeting process that utilizes local heating at solid tumor sites. Chung et al.

teach that the thermo-response is expected to exhibit multiple targeting functions: a passive and a stimuli-responsive targeting mechanism, plus the therapeutic effect of hyperthermia by local heating, see p. 94 1st col. Chung et al. teach that hyperthermia enhances the cytotoxicity of some anticancer drugs by synergistic effects, see p. 94- 2nd col. Chung et al. teach that thermo-sensitive lipsosomes have been used to achieve targeted drug delivery, see p. 94- 2nd col.

Jordan et al. teach that hyperthermia intensifies the efficacy of radiation and/or chemotherapy, see pp.118-119, Introduction and state of the art. Jordan et al. teach that ferromagnetic seeds can be used to induce localized hyperthermia with AC magnetic field of 25-50 kHz, see p. 119-2nd col. Jordan et al. teach using magnetic nanoparticles to induce hyperthermia in tumors with a device using a 100 kHz AC magnetic field, see section 3, pp. 120-124 and Fig. 2-3.

Tannock teaches that it has become common practice to treat cancer patients with multiple anti-cancer agents to enhance the tumor response over that of the individual agents. See p. 352-2nd col.., p. 353-1st col., p. 357- 2nd col. and Table 19.3. Tannock teaches that improvements in clinical chemotherapy have depended largely on the use of drugs in combination. See p. 338.

It would have been *prima facie* obvious at the time the invention was made and one of skill in the art would have been motivated to combine the teachings of Krauss et al. and Chung et al. and coat the nanoparticles with the thermo-sensitive co-polymers bound to the medicine/cytotoxin of Chung et al. to provide greater control of the timing of the release of the drug upon providing an appropriate increase in temperature by magnetic field induced hyperthermia. Furthermore, one would have been motivated to use a heat induced drug release

because Jordan et al. and Chung et al. teach hyperthermia intensifies the efficacy of radiation and/or chemotherapy. Additionally, it would have been *prima facie* obvious at the time the invention was made and one of skill in the art would have be motivated to use an AC magnetic field in the frequency range of 1 KHz-5MHz because Jordan et al. teach that AC magnetic fields in this range are routinely used in the art for the induction of magnetic hyperthermia. Additionally, one of skill in the art would have been motivated to treat with heat and chemotherapy, because Tannock teaches that it is common practice to treat cancer patients with multiple anti-cancer agents to get an enhanced anti-tumor response and Jordan et al. teach that hyperthermia intensifies the efficacy of chemotherapy.

Furthermore, it would have been obvious to use MRI imaging to confirm the contact of the particles to the target cell because Krauss et al. teach the use of MRI for detection and it would have been a known option within the technical grasp on one of skill in the art. In KSR International Co. v. Teleflex Inc., the U.S. Supreme court determined that "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under §103." *KSR International Co. v. Teleflex Inc.,* 82 USPQ2d 1385 (U.S. 2007). Thus, to use the known technique of MRI would have been obvious in view of the art given that it was a known option within the technical grasp on one of skill in the art.

5. Claims 3, 4, 13, and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over USPN 6,470,220 (Krauss et al. Oct. 22, 2002) evidenced by World Health Organization (What are electromagnetic fields?, 2010), as applied to claims 1, 2, 5-9, 15, 21, and 24 above, in view of USPN 6,231,496 (Wilk et al. May 15, 2001, previously cited) and in view of Tannock, I.F. (*Experimental Chemotherapy*, Ch. 19-p. 338 and 352-359, in The Basic Science Of Oncology Tannock and Hill, eds., New York 1992).

Krauss et al. teach as set forth above, and teach that MRI has potential for breast cancer detection. See col. 1. Krauss et al. does not teach delivery of medication, magnetic nanoparticles elongated long one dimension or confirming the contact with MRI imaging.

USPN 6,231,496 teach using magnetized metal particles that are advantageously tapered to form a sharp end for sterilization and cancer treatment by injecting the particles and orienting the particles with a magnet and pulling them into the tissue with a magnet. See cols. 1 and 2 and claims 1-21. USPN 6,231,496 teaches coating the particles with an irritant for treatment and antibiotics and anti-growth factor. See col. 7-lines 1-5 and claims 1-21

Tannock teaches that it has become common practice to treat cancer patients with multiple anti-cancer agents to enhance the tumor response over that of the individual agents. See p. 352-2nd col.., p. 353-1st col., p. 357- 2nd col. and Table 19.3. Tannock teaches that improvements in clinical chemotherapy have depended largely on the use of drugs in combination. See p. 338.

It would have been *prima facie* obvious at the time the invention was made and one of skill in the art would have be motivated to combine the teachings of Krauss et al. and USPN 6,231,496, and make and use elongated magnetic nano-particles that have a tapered or sharp end

as described by USPN 6,231,496 to enhance the shearing effect of cell disruption of the method Krauss et al. Furthermore, the addition of medication/cytotoxin to the particles for treatment and injection of the particles would have been obvious as the coating particles with medicine like antibiotics for treatment are routine method is the art for medical treatment as taught by USPN 6,231,496. Additionally, one of skill in the art would have been motivated to treat with heat and chemotherapy, because Tannock teaches that it is common practice to treat cancer patients with multiple anti-cancer agents to get an enhanced anti-tumor response.

Furthermore, it would have been obvious to use MRI imaging to confirm the contact of the particles to the target cell because Krauss et al. teach the use of MRI for detection and it would have been a known option within the technical grasp on one of skill in the art. In KSR International Co. v. Teleflex Inc., the U.S. Supreme court determined that "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under §103." *KSR International Co. v. Teleflex Inc.,* 82 USPQ2d 1385 (U.S. 2007). Thus, to use the known technique of MRI would have been obvious in view of the art given that it was a known option within the technical grasp on one of skill in the art.

6. Claims 12, 13 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over USPN 6,470,220 (Krauss et al. Oct. 22, 2002) evidenced by World Health Organization (What are electromagnetic fields?, 2010), as applied to claims 1, 2, 5-9, 15, 21, and 24 above, in

view of USPN 6,514,481 (Prasad et al. published 2/4/2003, effective filing date 11/22/1999, previously cited).

Krauss et al. teach as set forth above, and teach that MRI has potential for breast cancer detection. See col. 1. Krauss et al. does not teach attach molecules to stimulated endocytosis of the target cell and magnetic nanoparticles elongated long one dimension, or confirming the contact with MRI imaging.

USPN 6,514,481 teaches the lysis of a targeted cell with magnetic nanoparticles coated with biocompatible targeting peptides/ LHRH and a silica (silicon dioxide, See Dorland's Medical Dictionary for Healthcare Consumers (silica 2007)) shell by application of a magnetic field that moves the particles out of the cells. See claims 1-21, Example 4, and Fig. 6. USPN 6,514,481 teaches injection of nanoparticles into tissue for tumor treatment. See col. 1-lines 35-50. USPN 6,514,481 teaches that the LHRH magnetic particles are taken up by endocytosis. See col. 7-lines 20-25 and Examples 3. USPN 6,514,481 teaches that the particles are elongated along one dimension. See Fig. 2. USPN 6,514,481 teaches confirming the contact of the particles to the target cells prior to apply the magnetic field. See Examples 3 and 4.

It would have been *prima facie* obvious at the time the invention was made and one of skill in the art would have be motivated to combine the teachings of Krauss et al. and USPN 6,514,481 and use nanoparticles like those taught by USPN 6,514,48 coated with LHRH to stimulate endocytosis of the particles because USPN 6,514,481 teaches that direct contact or internalization of the particles is required for cytolysis and USPN 6,514,481 teaches using the LHRH to target the breast tumor cells, which Krauss et al. also contemplates treating. See Col. 7 and claims of USPN 6,514,481 and *Field of the Invention* of Krauss et al. Furthermore, an

internalized particle would not be shed from the cell and cause more damage by being in direct contact with the internal structures of the cell.

Furthermore, it would have been obvious to use MRI imaging to confirm the contact of the particles to the target cell because Krauss et al. teach the use of MRI for detection and it would have been a known option within the technical grasp on one of skill in the art. In KSR International Co. v. Teleflex Inc., the U.S. Supreme court determined that "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under §103." *KSR International Co. v. Teleflex Inc.,* 82 USPQ2d 1385 (U.S. 2007). Thus, to use the known technique of MRI would have been obvious in view of the art given that it was a known option within the technical grasp on one of skill in the art.

7. Claims 3, 4, 10, 11, and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over USPN 6,470,220 (Krauss et al. Oct. 22, 2002) evidenced by World Health Organization (What are electromagnetic fields?, 2010), as applied to claims 1, 2, 5-9, 15, 21, and 24 above, in view of Alexiou et al. (Cancer Research Dec. 2000, 60: 6641-6648, previously cited), and in view of Alexiou et al. (J. Drug Targeting, April 2003, 11: 139-149, previously cited) and in view of Tannock, I.F. (*Experimental Chemotherapy*, Ch. 19-p. 338 and 352-359, in The Basic Science Of Oncology Tannock and Hill, eds., New York 1992).

Krauss et al. teaches as set forth above, but does not teach delivery of medication, magnetic navigation, magnetic transfection, and MRI confirmation of the contact of the particles with the target cell

Alexiou et al. (2000) teach using magnetic nanoparticles surrounded by starch polymers bound to mitoxantrone (MTX) a chemotherapeutic agents that inhibits DNA and RNA synthesis to treat squamous cell carcinoma by magnetically targeting the MTX- magnetic nanoparticles to the tumors, see Abstract, Materials and Methods, and Figures. Alexiou et al. (2000) teach administering the nanoparticles by intravenous intra-arterial infusion, see Table 2. Alexiou et al. (2000) teach that the magnetic particles can be modified with monoclonal antibodies, lectins, peptides, hormones, or genes to make delivery of the compounds more efficient and highly specific, see p. 6648-1st col. Alexiou et al. teach localizing the magnetic particles with MRI after application of the magnetic field, see Fig. 16.

Alexiou et al. (2003) teach that magnetic drug targeting leads to uptake of the particles by cells, see Figure 3 and 4. Thus, the method of Alexiou et al (2000) is a method of magnetic transfection.

Tannock teaches that it has become common practice to treat cancer patients with multiple anti-cancer agents to enhance the tumor response over that of the individual agents. See p. 352-2nd col.., p. 353-1st col., p. 357- 2nd col. and Table 19.3. Tannock teaches that improvements in clinical chemotherapy have depended largely on the use of drugs in combination. See p. 338.

It would have been *prima facie* obvious at the time the invention was made and one of skill in the art would have be motivated to combine the teachings of Krauss et al. and Alexiou et

al. (2000) and Alexiou et al. (2003) and magnetically direct the nanoparticles to the cell and magnetically transfect the particles after injection because Alexiou et al. (2000) teach that magnetic drug targeting offers a unique opportunity to treat malignant tumors loco-regionally without systemic toxicity and magnetic targeting makes make delivery of the compounds more efficient and highly specific . See Abstract and p. 6648-1st col. Furthermore, it would have been *prima facie* obvious at the time the invention was made and one of skill in the art would have been motivated to confirm the adjacency of the magnetic nano-particles loaded with medication/cytotoxit in to the tumors using MRI to ensure the proper localization of the magnetic particles to the disease tumor tissue before induction of magnetic field to prevent to prevent damage to normal tissues if the nano-particles have not been properly localized. Additionally, one of skill in the art would have been motivated to treat with heat and chemotherapeutics taught by the art in combination, because Tannock teaches that it is common practice to treat cancer patients with multiple anti-cancer agents to get an enhanced anti-tumor response. Thus, given the above, one of skill in the art would have been motivated with a reasonable expectation of success to make and used the claimed method.

8. All other objections and rejections recited in of December 30, 2009 are withdrawn.

9. No claims allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to PETER J. REDDIG whose telephone number is (571)272-9031. The examiner can normally be reached on M-F 8:30 a.m.-5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Misook Yu can be reached on (571) 272-0839. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Peter J Reddig/
Primary Examiner, Art Unit 1642